REMARKS

The rejections of the claims will be addressed in the order in which they appear in the Office Action.

A. Rejection Under 35 U.S.C. § 112, Second Paragraph

The office action objected to the previous language of the claims which recited "wherein said synthetic polypeptide is prepared by chemical synthesis." In order to avoid what is essentially a semantic argument, that terminology has been deleted from the claims. The term "synthetic peptide" which appears in the claims (and has appeared in the specification from the first parent application, Serial No. 667,501) had a clear-cut, definite meaning at the time parent application Serial No. 667,501 was filed October 31, 1984 and continues to have that same meaning. The prior art is replete with examples which demonstrate that the term "synthetic peptide" means a peptide prepared by chemical synthesis.

The attached declaration of Assistant Professor John A.T. Young of Harvard Medical School (Attachment A) demonstrates that publications both before and after the October 31, 1984 filing date of the parent '501 application routinely employed the term " synthetic peptide" to refer to a peptide synthesized by chemical means (Young ¶ 4, 5)[1] Dr. Young cites 20 representative publications having a date before October 31, 1984 which provide scientific support for his statement. In addition, the prior art often made a clear distinction between synthetic peptides and peptides fragments generated by other

[1]On this, and other issues, Dr. Young's Declaration does not merely present an unsupported conclusion. On the contrary, in each instance Dr. Young provides reasoning or authorities which support his statements. A copy of each of the references referred to by Dr. Young is being supplied separately.

means such as cleavage of the natural protein. Dr. Young cites no less than eight publications which make that distinction. (Young ¶ 6).

The publications cited in Dr. Young's affidavit not only establish the clear meaning for the term "synthetic peptide" but they also demonstrate that the prior art was fully capable of generating synthetic peptides containing as many as 40 amino acids. (Young ¶ 7) For example, Altman 1984, Barkas 1984, Green 1983, Jacob 1983, Shi 1984, and Rothbard 1984 all employed synthetic peptides containing 15-20 amino acid residues. Dale 1983, Hirayama 1982, Milchizedek 1984 and Muller 1983 employed synthetic peptides containing 20-25 amino acid residues, Bellet 1984 employed a 37 amino acid residue synthetic peptide and Puett disclosed a 40 amino acid synthetic polypeptide.[2]

When the '501 application spoke of "synthetic peptides," (see page 3, line 15) it was speaking to an art which not only knew that the peptides referred to were made by chemical synthesis but which was also able to make such peptides of considerable length. The same holds true today.

B. Rejection Under 35 U.S.C. §112, First Paragraph

The claims stand rejected as failing to provide an enabling disclosure regarding obtaining synthetic polypeptides for use in the claimed immunoassays. That rejection is respectfully traversed. The claims are enabled and, indeed, were enabled by the first application, Serial No. 667,501, filed October 31, 1984.

Precedent regarding enablement includes the following:

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[2]The full cite of the publications is contained in Exhibit 2 of the Young Declaration.

1. A patent need not teach, and preferably omits, what is well known in the art. Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986).

2. The disclosure of an application embraces not only what is expressly set forth in words or drawings, but what would be understood by persons skilled in the art. In re Chilowsky, 108 USPQ 321, 324 (CCPA 1956).

3. Relevant prior art teachings which establish what would be understood by persons skilled in the art need not be specifically identified in the specification. Applicant must establish, however, that one skilled in the art "would reasonably be expected to check the source which the applicant relies upon to complete his disclosure and would be able to locate the information with no more than reasonable diligence." In re Howarth, 210 USPQ 689, 693 (CCPA 1981).

4. The enablement standard of 35 U.S.C. § 112 allows for experimentation. Indeed, even "a considerable amount of experimentation is permissible if it is merely routine." In re Wands, 8 USPQ 2d 1400, 1404 (Fed. Cir. 1988).

The following remarks are in addition to those contained in the response filed October 2, 1995.

1. **Assays and Use of the Synthetic Polypeptides**

The specification from the outset has specifically taught that the polypeptides of the invention, including "immunologically active fragments" may be used as diagnostic reagents and has provided a representative list of immunogenic assays in which they

could be used. Representative statements in the October, 1984 '501 specification include the following:[3]

> "The polypeptides or immunogenically active fragments thereof, may find use as diagnostic reagents, being used in labeled or unlabeled form..." (p. 11, lines 5-7) [p. 22, lines 1-3]
>
> * * * * *
>
> "The expression products of the *env* or *gag* genes and immunogenic fragments thereof having immunogenic sites may be used for screening antisera from patients' blood to determine whether antibodies are present which bind to hTLR antigens. A wide variety of assay techniques can be employed, involving labeled or unlabeled antigens. The label may be fluorescers, radionuclides, enzymes, chemiluminescers, magnetic particles, enzyme substrates, cofactors or inhibitors, ligands, or the like." (p. 14, lines 17-26) [page 26, lines 9-23]
>
> * * * * *
>
> "A particularly convenient technique is to bind the antigen to a support and contact the blood sample with the antigen. After washing the support to remove non-specifically bound antisera, labeled antibodies to human Ig are added and specifically bound label determined." (p. 14, lines 27-32) [p. 26, lines 24-32]
>
> * * * * *
>
> "For diagnosis, the antibodies can be used in conventional ways to detect hTLR in a clinical sample." (p. 15, lines 2-4) [p. 28, lines 25-27]

Speaking to the art, the 1984 specification taught that the polypeptides or immunogenically active fragments could be used in a wide variety of assays to detect

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[3]Citations in [ ] are to comparable statements which still appear in the pending application.

the presence of antibodies to hTLR (HIV) involving both labeled or unlabeled antigens.[4] No less than nine different possible labels are specifically identified. Pointedly, the specification makes no attempt to limit the nature of the immunoassay which can be employed. On the contrary, the specification makes it clear that immunoassays generally can be employed.

There is no legitimate basis to attack the 1984 specification as in any way lacking a description or lacking a fully enabling teaching regarding immunoassays for detecting antibodies. Indeed, it is not clear that the Office Action attempts to do so. The Office Action at page 4, however, asserts that there "is no suggestion....in the specification as to how to proceed to use the synthetic peptides" referred to at page 3 of the '501 specification. That assertion is respectfully traversed.

As the Office Action recognizes, page 3 of the '501 specification specifically contemplates the production of synthetic peptides. That teaching is <u>not</u> in a vacuum. Having made the synthetic peptide one would be directly led <u>by the specification</u> to use that peptide in the very procedures taught by the specification - an immunoassay to detect antibodies to HIV and as a vaccine. (Young ¶ 9) That conclusion is inescapable. It does the concept of one skilled in the art a serious disservice to suggest that one, having read the '501 specification and followed its direction to make a synthetic peptide, would then stand bewildered as how to use that peptide.

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[4]While reference in the above passages at times is to polypeptides expressed by *env* or *gag* genes, the description is also generic to "antigen" or "antigenic polypeptide," which the '501 specification teaches at page 3 can be made synthetically.

The Office Action, further asserts that there were no assays employing a synthetic peptide known in the art at the time of filing of the parent application in October, 1984. Contrary to that assertion of the Office Action, the immunoassays described in the October, 1984 specification, as well as still others employing synthetic peptides, were known in the art.

Synthetic peptides had been used prior to October 31, 1984 in the general types of immunoassays taught by the specification. (Young ¶ 8) Immunoassays employing synthetic peptides included ELISA which employed peptides immobilized on microtiter plates, test sera, and enzyme-coupled secondary antibodies (e.g. Altman 1984, Green 1983, Wabuke-Bunoti 1984, Rothbard 1984, Bellet 1984, Jolivet 1983). The prior art techniques also included solid-phase radioimmunoassays that employed immobilized synthetic peptides, test sera, and ^{125}I-labeled protein A (Rothbard 1984, Pacella 1983, Morrow 1984, Jacob 1983). Other methods were also known in the art in 1984 for detecting specific interactions between synthetic peptides and antibodies, including radioimmunoassays that employed radioactively-labeled peptides (e.g. Tamura 1982, Barkas 1984, Hintz 1982, Shi 1984, Rougon 1984). No less than 14 references support Dr. Young's statement.

The specification itself provides more than adequate guidance regarding use of antigenic peptides of the invention in immunoassays. The specification specifically teaches that synthetic polypeptides can be used in the claimed immunoassays and the prior art demonstrates that use of synthetic polypeptides in immunoassays was known.

2. Identification of Antigenic Synthetic Peptides

There were at least two separate art-recognized techniques in 1984 for the identification of antigens.

a. Hydrophilicity Method

The hydrophilicity method as taught by the Hopp et al. references[5] provided one technique which enabled the identification of a synthetic polypeptide antigen in 1984. (Young ¶ 10)

The threshold test as to whether the disclosure of a prior reference qualifies as knowledge of the prior art is whether the source is one that could be expected to be checked and whether the article would be located with no more than reasonable diligence. (In re Howarth, 210 USPQ 689, 693 (CCPA 1981)). The answer to both questions is a clear-cut yes.

The Hopp et al. technique was published in leading publications (PNAS and Mol. Immun.) which most certainly would be checked by one skilled in the art. While probably unnecessary, that well understood fact is attested to by Dr. Young. (Decl. ¶ 4) Moreover, one need look no further than the titles ("Prediction of Protein Antigenic Determinants. . ." and ". . . Program for Predicting Antigenic Determinants") to confirm that anyone interested in antigenic determinants would immediately be led to them.

The 1983 Hopp et al. article taught that the described technique was suitable for identifying epitopes on a number of different antigens. Actual experience through the

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[5]Hopp, et al., *"Prediction of Protein Antigenic Determinants from Amino Acid Sequences," Proc. Natl. Acad. Sci.*, 78, No. 6, pp. 3824-3828 (June 1981); Hopp et al., *"A Computer Program for Predicting Protein Antigenic Determinants," Mol. Immunol.*, 30, No. 4, pp. 483-489 (1983)

years has also shown that the technique is successful. As Hopp (1983)[6] stated "The Hopp and Woods hydrophilicity method for locating antigenic determinants was published in 1981. In the years since then, the method has been used widely and has played a vital role in many antigenic studies." The directions are clear and require no more than routine skill to follow. (See Young ¶ 10).

In order to test its usefulness, Dr. Young employed the Hopp technique it to identify three epitopes in the envelope region of HIV. (Young ¶ 11) The correlation is striking between the predicted epitopes identified by Dr. Young using the Hopp technique and the synthetic peptides later determined by others to include an epitope.

aa 505-510 - Dr. John Young

497-509 - Krowka (1991)
507-518 - Streckert (1992)
495-516 - Mescheryokova (1993)

aa - 653-658 - Dr. John Young

647-661 - Brollden (1992)
652-666 - Broliden (1992)
650-667 - Goudsmit (1990)[7]
649-662 - Krowka (1991)

aa - 738-743 - Dr. John Young

732-746 - Broliden (1992)
732-748 - Goudsmit (1990)
735-752 - Kennedy (1986)

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[6]Hopp, et al., *"Retrospective: 12 Years of Antigenic Determinant Predictions, and More," Peptide Research*, 6(4):183-190 (1983) (Of Record)

[7]The amino acid numbering system used in the various references varies because the exact number of residues differs somewhat among HIV isolates. For example, Streckert's amino acids 498-509 correspond to amino acids 507-518 in Figure 4. The numbers given here refer to the location of the reference's sequence in Figure 4.

Dr. Young has also identified epitopes in the Gag region (¶12).

Hopp 1981 identified the hydrophilicity value for each amino acid and also provided specific directions regarding the method by which those values are applied. The '501 application provides (1) the nucleotide and amino acid sequence of the envelope domain of HIV and (2) the important teaching that synthetic peptides can be used in an immunoassay. Confirming antigenicity by testing in an immunoassay against antiserum of a patient known to be HIV positive was also routine as demonstrated, inter alia, by the Hopp et al. publications themselves. (Young ¶ 10-12). The publications cited by Dr. Young in Paragraph 7 of his Declaration demonstrate that the actual preparation of synthetic peptides was most certainly within the skill of the art. The Hopp et al. technique thus "enabled" the identification of synthetic polypeptide antigens for use in the claimed immunoassays.

The Office Action asserts that "reactive with antibodies" is not the same as being "immunogenic". Both the Hopp publications and the present application, however, are directed to epitopes that are tested to ensure that they are identified by antibodies raised by infected humans. That very test ensures that the epitopes are, in fact, immunogenic.

b. Panels of Synthetic Peptides

Another approach for determining antigenic polypeptide fragments known in the art was to generate one or a panel of several synthetic peptides derived from a polypeptide sequence and test each peptide for antibody reactivity. The parent '501 application provides both the DNA and the peptide sequence of the envelope region and,

therefore, fully enables such technique. One of ordinary skill in the art in 1984 was easily able to generate panels of synthetic peptides from a protein (Young ¶ 13-16).

A related technique for determining antigenic polypeptide fragments taught by Geysen[8] and expressly said by Geysen to be applicable to a broad spectrum of proteins is aptly characterized by the Office Action as one "which was to prove extremely useful." This "extremely useful" technique, published in the high profile journal, *Proceedings of the National Academy of Sciences*, is brushed aside in the Office Action, based on the assertion that "there is nothing of record to suggest that it would have been regarded as routine experimentation" in 1984.

As a threshold matter, Geysen et al. was published in a source which could be expected to be checked by one skilled in the art and the article most certainly would stand out. (Young, Decl. ¶ 4) The *Proceedings of the National Academy of Sciences* is a world-recognized leading scientific journal. Once again, one need not look farther than the Geysen title to be assured that one interested in locating synthetic peptide epitopes of a virus would find Geysen. Surely, an article entitled *"Use of Peptide Synthesis to Probe Viral Antigens for Epitopes..."* would be irresistible for anyone interested in the identification of viral antigens. The Geysen article was in a leading scientific journal and its title was squarely on target.

The Office Action appears to focus on how one skilled in the art would have "regarded" the technique in 1984. That is not the test. The test is whether the prior art

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[8]Geysen, et al., *"Use of Peptide Synthesis to Probe Viral Antigens for Epitopes to a Resolution of Single Amino Acid," Proc. Natl. Acad. Sci.*, 81:3998-4002 (July 1984)

"enabled" the protein of the invention and, the Office Action concedes that the Geysen *et al.* technique is in fact, useful.

The prior art was capable of synthesizing peptides of considerable length. (Young ¶ 4) The 1984 parent application provides the nucleotide and amino acid sequence of the envelope domain of HIV and the important teaching that synthetic peptides can be used in immunoassays. Geysen et al. informed one skilled in the art how to identify viral epitopes using procedures then available to the art. Following the "extremely useful" Geysen teaching, epitopes would, in fact, be identified.

The inescapable conclusion is that the known, published Geysen et al. technique "enabled" the identification of the synthetic polypeptide antigens for use in the claimed immunoassays.[9]

3. The Term "Immunogenic" In The Claims

The objection to insertion of the term "immunogenic" into the claims appears to be little more than a restatement of the objection based on an asserted inability to identify antigens. That objection is fully addressed and refuted in Section B.2.

The term "immunogenic" appears in the October, 1984 specification in haec verba as well as in substance. See, for example, page 14, line 18 ("immunogenic fragments") and page 11, line 5 ("immunogenically active fragments").

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[9]Dr. Rob Meleon, one of the authors of the Geysen, et al. article, filed a self-serving declaration in an EPO opposition involving different subject matter. Dr. Meleon's objection in that case focussed in part on the use of short epitopes (e.g. - 8 amino acids - ¶ 22). In the present case, the '501 specification teaches that at least 15 amino acids (corresponding to 45 bp) preferably be used. Dr. Meleon's declaration re-enforced the position taken here on behalf of Luciw when he stated that linear epitopes "may be mapped using peptides of 12 amino acids in length." (¶ 15) (A copy of the Meleon Declaration is being filed as part of the IDS.)

4. Summary

The October 31, 1984 parent application enabled one skilled in the art to identify the claimed antigenic synthetic polypeptides, to make such polypeptides and to use them in a wide variety of immunoassays. Pointedly, in litigation between Chiron and Abbott Laboratories involving Luciw U.S. Patent 5,156,949, Abbott vigorously asserted that the October 31, 1984 parent application did not enable an immunoassay employing recombinant envelope antigens. The court considered Abbott's arguments and evidence, then ruled against Abbott. The court held that "no reasonable jury could find for Abbott on this affirmative defense". (See Amended Memorandum and Order re Defense of Enablement, C-93-4380, as part of the IDS.)

C. Prior Art

1. Cited Art

The references relied on by the Office Action have effective dates later than the October 31, 1984 filing date of parent application Serial No. 06/667,501. Because the claims are, in fact, supported by the parent application, the art rejections must fail.

2. Documents Discussed at Interview

At the interview of January 29, 1997, three documents (Schupbach et al., Montagnier et al. and Chang) were discussed. These documents have publication or filing dates prior to the filing of the '501 parent on October 31, 1984 and purport to have identified the AIDS causative agent. None of these documents adversely impacts applicants' claims.

In order to place these and other prior art documents in context, a brief review of the state of the art is in order.

In October 1984, the nature of the virus which caused AIDS was very poorly understood. Contemporaneous publications prior to October 31, 1984 attest to the confusion surrounding the identity of HIV. For example, Montagnier's group postulated that HIV was related to equine infectious anemia virus ("EIAV"). Montagnier, et al., *Science*, 225, 63-66 (1984) Gallo's group at NIH, on the other hand, confidently announced in several 1984 publications that the HIV virus (HTLV-III) is related to HTLV-I and HTLV-II and "HTLV-III is clearly distinguishable from HTLV-I and HTLV-II but is also significantly related to both viruses. HTLV-III is thus a true member of the HTLV family" (Schupbach, et al. *Science*, 224, pp. 503-505 (1984). Indeed, the Gallo group announced that there was extensive antibody cross-reactivity and sequence homology between HTLV-III and HTLV-I and II.(Schupbach, *Id.*; *Arya et al., Science*, 225, pp. 927-930 (1984); Sarngadharan *et al., Science*, 224, pp. 506-508 (1984) The confidence of the Gallo pronouncement was matched only by its inaccuracy. HIV is not related to HTLV-I and II and there is not extensive cross-reactivity.[10]

Further, the difficulty of growing a culture of cells containing the virus presented a very real obstacle to the art attempting to generate sufficient quantities of HIV for detailed characterization because the virus is cytopathic. (Young ¶17) The Gallo group gave voice to this "major obstacle" in Popovic, et al., *Science*, 224:497-500 (1984):

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[10]Gallo later conceded the error, postulating that the cells were probably co-infected with HIV and an HTLV. See: Gallo, "Virus Hunting AIDS Cancer and the Human Retrovirus, *New Republic Book*, 1991, pp. 143, 152.

> "The transient expression of cytopathic variants of HTLV in cells from AIDS patients and the previous lack of a cell system that could maintain growth and still be susceptible to and permissive for the virus represented a major obstacle in detection, isolation, and elucidation of the precise causative agent of AIDS."

Those persons who did ultimately succeed in maintaining a cell culture did so by discovering a specific cell line and culture conditions which were specific to that cell line. Compounding the already daunting task of virus characterization was the well-known variability of the virus and, no sequence for any isolate had been published by October 31, 1984.

Schupbach *et al., Science*, 224, 503-505 (May 4, 1984)

Schupbach *et al.* (Gallo is a co-author) purport to have identified a band on a gel which represented an HTLV-III protein fragment. No information regarding either DNA or polypeptide sequence is provided. The Schupbach blot would not have represented sufficient material to determine the amino acid sequence, and thereby make a synthetic envelope antigen for use in the claimed immunoassay. (Young, ¶ 17) Pointedly, the cell line employed by Schupbach *et al.* was not available to the general public nor was it described in sufficient detail to allow another worker to obtain it. Therefore, the Schupbach experimental work could not have been repeated by others in the art. (Young ¶ 17). Indeed, the conclusion that HIV was a "true member" of the HTLV family with significant antibody cross-reactivity and sequence homology coming from an important research group was a red herring that actually led away from the discovery of the true HIV DNA and polypeptide sequences. (Young, ¶18-19)

Montagnier, *Science*, 225, 63-66 (July 1984)

Like Schupbach, Montagnier et al. reported only bands on a gel which purport to represent a fragment from the AIDS causative agent. Once again the bands would not provide sufficient material to determine the amino acid sequence and, the cell lines used by Montagnier et al. were not available to the general public. (Young ¶17) Finally, like Schupbach, Montagnier provided no DNA or polypeptide sequence. (Young ¶17)

Further, the focus of the article by Montagnier et al. is primarily on a band identified as "p25." We now know that such a band is in the *gag* region of HIV, not the *env* region. Montagnier's disclosure would not have enabled one skilled in the art to practice the presently claimed invention. (Young ¶17)[11]

In retrospect it seems clear that, given the intense scientific competition regarding the identification of the AIDS causative agent, neither the Gallo group nor the Montagnier group was anxious to make a disclosure which would enable those skilled in the art.

Chang Application 659,339 filed October 10, 1984[12]

The Chang specification is a confusing document that includes what is said to be a partial HIV sequence in Figure 3. Figure 3 does not indicate the location of the DNA within the HIV genome, nor indicate which portions of the nucleotide sequence

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[11]Montagnier U.S. Patent 4,708,818 claims to be a division of U.S. application Serial No. 558,109 filed December 5, 1983. The '818 patent, however, is essentially cumulative to the later Montagnier paper.

[12]The Chang application is not a 35 U.S.C. §102(e) reference because no U.S. patent to Chang has issued. Chang is involved, however, in Interference No. 103,659 with U.S. Patent 5,156,949 to Luciw et al.

represents the nucleotide sequence of the *env* gene, stating only that the sequence "encompasses" the *env* gene. There is no indication of amino acids encoded by the nucleotide sequence, nor is there any indication of reading frame.

While Chang Figure 3 purports to disclose the DNA sequence which encompasses the *env* region of HTLV-III, the *env* region is misidentified by Chang. (Young ¶20-23) The DNA sequence provided by Chang, insofar as discernible from the fragmented Figure 3 sequence contained in the certified copy of application Serial No. 659,339 provided to Chiron,[13] includes a portion of the *pol* gene, the *sor* gene and only about one-third of the envelope gene. (Young ¶21) Only a small portion of the nucleotide sequences in Figure 3 represent envelope sequence which can be in the correct reading frame. (Young ¶22) There is an extra "A" at position 2437 so that a reading frame shift will occur and all the DNA sequence thereafter is out of correct reading frame. (Young ¶22)

Following the Gallo fallacy that HTLV-III was a "true member" of the HTLV family, Chang misidentifies the target of the chase as a "p41" - the "presumed envelope antigen of HTLV-III." (p. 5, lines 11-31). The surface antigen of HIV is, of course, not [g]p 41(sic) but gp 120 (Young ¶19), and the Env precursor is gp160. Thus, Chang was looking for the wrong sized open reading frame.

The general description of the Chang specification does not rescue the otherwise erroneous disclosure. On the contrary, it adds still further to the confusion. For example, the embodiment described at page 7, line 3 to page 8, line 31, refers to the restriction sites of Figure 1 and 2 to produce fragments, and directs that "DNA fragments

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[13]We understand that the Chang application has been lost by the Patent Office.

of approximately 200-500 bp are isolated from agarose gel." The fragments shown in Figures 1 and 2, however, are of kilobase length, not 200-500 bp. (See eg: page 9, lines 16-17). The confusion does not even end there. The passage at page 9, lines 11-19 describes the "1.0 kb $EcoR_1$ - $EcoR_1$" fragment as being part of the *env* gene as shown in Figure 1b. We now know that the entire $EcoR_1$ - $EcoR_1$ fragment is outside the *env* region. Note also that the Bgl II-Bgl II fragment of Figure 1 is not in the same location as shown in Figure 2, yet both Figures are said to be a representation of HTLV-III DNA (p. 4, lines 21-30).

The cell line with which Chang worked is not identified in the application so that there was no basis for one skilled in the art to unscramble the hopeless confusion created by the Chang specification. Pointedly, the court, in *Chiron v. Abbott Laboratories*, C-93-4380, granted Summary Judgement (over Abbott's vigorous assertion to the contrary) that the Chang disclosure was not enabling.[14] The relevant portions of the court's opinion regarding enablement are being filed as part of the IDS.

3. Summary

Applicants' parent application Serial No. 667,501 filed October 31, 1984 was the first disclosure of the complete sequence of an HIV isolate and the first accurate identification of the Env gene and reading frame, thus permitting the production of polypeptides with defined amino acid sequences for diagnostic and therapeutic purposes. That was no small accomplishment given the confusion in the art regarding the nature

[14]A detailed discussion of the many, many deficiencies of the Chang disclosure is contained in the Declaration of Dr. John Young filed in Interference No. 103,659 (attached as Attachment B).

of the AIDS causative agent and the "major obstacle" faced when attempting to culture infected cells. Chang is virtually irrefutable evidence that applicants' accurate identification of this HIV *env* gene and its reading frame was not within the ordinary skill of the art in October 1984.

Schupbach et al.'s showing of a blot hardly qualifies as an enabling disclosure of an amino acid and DNA sequence, information which is totally missing from the article. Montagnier is even less relevant. In any event, these publications were clearly available to Chang (e.g., Gallo, a co-inventor, is a co-author of Schupbach and was undoubtedly familiar with Montagnier's work) who failed in her efforts to identify the HIV *env* gene.

D. **Obviousness-type Double Patenting**

A terminal disclaimer will be filed upon receipt of a Notice of Allowability.

E. **Conclusion**

The pending claims are, and have been since the original parent, supported and enabled. Reconsideration and allowance of pending claims 60-67 are respectfully requested.

Respectfully submitted,

Dated: March 19, 1997

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